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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,785	10/03/2005	Marco Cattaruzza	DEBE:053US/10501498	1068

32425 7590 06/09/2008
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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
06/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,785	CATTARUZZA ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

The finality of the previous Office action has been withdrawn in view of the following new grounds of rejection.

The indicated allowability of claims 1 and 2 is withdrawn in view of newly discovered reference(s), retrieved during an updated sequence search, that are considered to read on the instantly claimed decoy and pharmaceutical composition thereof. Rejections based on the newly cited reference(s) follow.

Applicant's response filed 4/21/08 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2/1/08 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 5/1/08, claims 1-3 are pending and under examination.

Also acknowledged is Applicant's amendments to pages 8 and 14 of the specification. The amendments have been entered.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 2 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-19 of copending Application No. 10/526430. Although the conflicting claims are not identical, they are not patentably distinct from each other because conflicting application 10/526430 claims a pharmaceutical formulation comprising a nucleic acid and a nonsteroidal anti-inflammatory drug.

MPEP §804 provides that "...those portions of the specification which provide support for the patent claims may also be examined and considered when addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. *In re Vogel*, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in *Vogel* recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an

obvious variation of an embodiment disclosed in the patent which provides support for the patent claim.

35 USC 112, first paragraph, support for claims 11-19 of copending application 10/526430 finds that the "nucleic acid" may be a decoy oligonucleotide of the type comprising or identical to that now claimed. An updated STIC-Biotech sequence search of instant SEQ ID NO:17 finds that the double stranded oligonucleotides corresponding to SEQ ID Nos. 1, 2, 5, 6, 13, 14, 17, 18, and 37 each comprise instant SEQ ID NO:17. See selected alignments below.

Thus, given that the "nucleic acid" recited in claims 11-19 of 10/526430 may be any one of the decoy oligonucleotides disclosed in the 10/526430 specification, and given that the instantly claimed decoy is intended for pharmaceutical use to treat an inflammatory condition, such as arthritis, one of ordinary skill in the art would conclude that the invention defined in claims 1 and 2 is anticipated by, or would have been an obvious variation of, the invention defined in a claim in the conflicting application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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RESULT 3
US-10-526-430A-17
; Sequence 17, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT: WAGNER, ADREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: Patentin version 3.1
; SEQ ID NO 17
;   LENGTH: 16
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-17

  Query Match           100.0%;  Score 16;  DB 14;  Length 16;
  Best Local Similarity  100.0%;  Pred. No. 9e+02;
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```
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db          1 TCCCTGGCCGGCTGAC 16


RESULT 4
US-10-526-430A-18/c
; Sequence 18, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT:  WAGNER, ADREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 18
;   LENGTH: 16
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-18

  Query Match             100.0%;  Score 16;  DB 14;  Length 16;
  Best Local Similarity   100.0%;  Pred. No. 9e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db         16 TCCCTGGCCGGCTGAC 1


RESULT 8
US-10-526-430A-13
; Sequence 13, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT:  WAGNER, ADREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 13
;   LENGTH: 19
;   TYPE: DNA
;   ORGANISM: Artificial Sequence
;   FEATURE:
;   OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-13

  Query Match             100.0%;  Score 16;  DB 14;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 8.6e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db          4 TCCCTGGCCGGCTGAC 19


RESULT 9
US-10-526-430A-14/c
; Sequence 14, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT:  WAGNER, ADREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
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;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 14
;    LENGTH: 19
;    TYPE: DNA
;    ORGANISM: Artificial Sequence
;    FEATURE:
;    OTHER INFORMATION: Decoy-Oligonucleotide
US-10-526-430A-14

  Query Match             100.0%;  Score 16;  DB 14;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 8.6e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db         16 TCCCTGGCCGGCTGAC 1


RESULT 10
US-10-526-430A-37/c
; Sequence 37, Application US/10526430A
; Publication No. US20060258601A1
; GENERAL INFORMATION:
;  APPLICANT: HECKER, MARKUS
;  APPLICANT: WAGNER, ADREAS H.
;  TITLE OF INVENTION: Functional correction of the -786C/T-variance of the human eNOS-gene
;  FILE REFERENCE: DEBE:052US
;  CURRENT APPLICATION NUMBER: US/10/526,430A
;  CURRENT FILING DATE:  2005-03-01
;  PRIOR APPLICATION NUMBER: PCT/DE 03/02901
;  PRIOR FILING DATE: 2003-09-12
;  PRIOR APPLICATION NUMBER: DE 102 42 319
;  PRIOR FILING DATE: 2002-09-12
;  NUMBER OF SEQ ID NOS: 63
;  SOFTWARE: PatentIn version 3.1
; SEQ ID NO 37
;    LENGTH: 19
;    TYPE: DNA
;    ORGANISM: Artificial Sequence
;    FEATURE:
;    OTHER INFORMATION: DNA Oligonucleotide
US-10-526-430A-37

  Query Match             100.0%;  Score 16;  DB 14;  Length 19;
  Best Local Similarity   100.0%;  Pred. No. 8.6e+02;
  Matches   16;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TCCCTGGCCGGCTGAC 16
              ||||||||||||||||
Db         18 TCCCTGGCCGGCTGAC 3
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Claim Rejections - 35 USC § 112, first paragraph (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Upon further consideration of the state of the art at the time of filing, the lack of evidence reasonably correlating the in vitro data in the specification with any therapeutic effect, and the

art-recognized challenges and unpredictability associated with the delivery of nucleic acids to cells and tissues in vivo, particularly cells in the joints, there is sufficient reason to doubt whether sufficient direction and guidance was present at the time of filing to enable one of skill in the art to produce a therapeutic effect representative of treatment of rheumatoid arthritis or coronary heart disease in a patient.

Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claim is drawn to a method of treating coronary heart disease and rheumatoid arthritis by delivery of a decoy oligonucleotide comprising SEQ ID NO:17 and 18.

Therefore the invention requires delivery and uptake of a nucleic acid into cells and tissues in vivo in an amount necessary to produce a therapeutic effect, wherein said effect is directly relevant to symptoms and conditions associated with coronary heart disease and rheumatoid arthritis.

A careful review of the specification finds no in vivo working examples representative of the claimed method. No instances in the prior art are found describing the use of the claimed decoy to treat any disease. No nexus has been established between the biological effects mediated by the decoy in vitro and the therapeutic effect claimed in vivo.

The specification at page 38, Table 3, shows that a decoy oligonucleotide comprising SEQ ID NO:17 is capable of restoring the inhibitory effect of IL-10 on the CD154-induced IL-12 p40 mRNA expression in endothelial cells from donors with the -786 C/C genotype in the eNOS gene. The SNP is said to affect the amount of nitric oxide production of endothelial cells. IL-10 is said to play a role in eNOS expression. Applicant then concludes on the basis of these data and a proposed link between the -786C/C genotype and RA and CHD (Tables 1 and 2, pages 31-32), restoration of the anti-inflammatory activity of IL-10 in cells in vivo by administration of said decoy would be remedial to conditions associated with a host of inflammatory diseases, including rheumatoid arthritis and coronary heart disease.

However, there is no evidence suggesting that the biochemical effects observed in vitro in cultured cells would translate to a therapeutic effect in vivo in a subject in need. Applicant does not provide any evidence that the restorative effects observed in vitro with regard to p40 mRNA expression would correlate with any type of treatment effect in vivo. A sufficient link between

the biochemical pathway said to be altered by the decoy in cells in vitro and the effects representative of therapy in a person is absent. Instead, Applicant relies on complex array of facts and evidence available in the prior art and disclosed in the specification loosely correlating the activities of interleukins, various transcription factors, eNOS expression and the symptoms associated with arthritis and coronary heart disease.

The problem is that no direct nexus has been established between the biological effects observed in cells in vitro and the therapeutic effects claimed. How or if the in vitro effects would be manifested in a patient are completely unknown. Given the lack of complete understanding as to the many different factors that may potentially cause or contribute to RA and CHD in any patient, the presumption that the restoration of IL-10 activity in cells in vitro may be used to alleviate one or more symptoms associated with RA or CHP is speculative.

Additionally, the prior art is replete with evidence suggesting the delivery of nucleic acids to cells in vivo was challenging. Applicant provides no direction or guidance as to how or even whether the claimed decoys may be delivered into cells in vivo, particularly cells in the synovial lining, in an amount and for a sufficient time to produce a therapeutic effect. Depending on the mode, delivery itself may exacerbate the very symptoms the decoy is designed to alleviate. The disclosure provides no direction as to how to deliver the decoy so as to achieve the claimed effect. As a result, one of skill would have no assurance the claimed effects could be obtained without engaging in undue experimentation.

Furthermore, while the prior art suggests that nucleic acids may be delivered into the synovial lining by direct injection, the specification provides no evidence, guidance, or direction

as to how to deliver the decoy into synovial fluids or cells via systemic administration, which is a mode currently embraced by the claim. Moreover, the prior art suggests that non-viral delivery to cells in the synovium is low and viral-mediated delivery while feasible suffers from unreliable or short-lived expression of the transgene. See Ghivizzani et al. (2001) *DDT* 6:259-267, who state that RA has proven to be an exceedingly difficult disease to treat. "In general, high doses of drugs are necessary to achieve therapeutic levels in the joint, and many agents that are effective in providing symptomatic relief require repeated administration, often with unpleasant side effects." (page 259).

While the instant application reasonably identifies a potential molecular biological link between eNOS expression, the -786C/C genotype, and certain inflammatory diseases such as RA and CHD, the biochemical link and in vitro data represent nothing more than a starting point for further research, which would be necessary to establish whether the conditions of RA and CHD in a patient (e.g., animal model) would be effectively treated by administration of the instant decoy in the manner proposed by applicant.

Therefore, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LW
Examiner AU1635
May 27, 2008

/Sean R McGarry/
Primary Examiner, Art Unit 1635